

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IB/G-33347/ABCK GWL	FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/EP2004/010134	International filing date (day/month/year) 10.09.2004	Priority date (day/month/year) 11.09.2003	
International Patent Classification (IPC) or national classification and IPC C07D307/88			
Applicant SANDOZ AG et al.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 22.12.2005		Date of completion of this report 17.02.2006	
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Kyriakakou, G Telephone No. +49 89 2399-7835	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/010134

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-24 as originally filed

Claims, Numbers

1-25 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
- ☐ restricted the claims.
 - ☒ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-13, 22,23
	No: Claims	16-21,23,24
Inventive step (IS)	Yes: Claims	
	No: Claims	1-25
Industrial applicability (IA)	Yes: Claims	1-25
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/EP2004/010134

Re Item I

Basis of the report

The examination is being carried out on the following application documents:

Description:

Pages 1 to 24 as originally filed

Claims:

Nos. 1 to 15 as originally filed

Re Item IV

Lack of unity of invention

This Authority considers that there are 3. inventions covered by the claims indicated as follows:

I: Claims 1-13 directed to a process for the purification of mycophenolate mofetil.

II: Claims 14,15 directed to mycophenolate mofetil and claims 16-23. directed to a process of preparation of mycophenolate mofetil

III: Claims 24,25 directed to Oxalate of Mycophenolate mofetil

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows: Mycophenolate mofetil is a known compound. Furthermore its preparation and several salts of the compound are also known. The alternatives comprised by the present claims 1-25 relate therefore to a further development of the state of the art in different directions.

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Reference is made to the following documents

D1:WO-A-02100855

D2:WO-A-0034503

D3: US-A-4748173

D4: US-A-5247083

D5: WO-A- 95/07902

D6:US-A-4 686 234

D7:US-A-4 727 069

D8:EP-A-0 281 713

2. Novelty(Art.33(2)PCT)

2.1 The present claims 1-13 relate to a process of purification of mycophenolate mofetil whereby a solution or suspension of mycophenolate mofetil(I) is treated with a primary or secondary amine. D1 and D4 disclose the preparation of high purity mycophenolate mofetil by esterification under azeotropic separation of water(see D1 example 3 and D4 example 1)

D2 discloses the preparation of high purity mycophenolate mofetil by esterification without the use of an organic solvent and a chemical catalyst or under mild conditions using enzymes(see page 2 lines 5-11)

The prior art document D3 discloses the preparation of base addition salts with amines of mycophenolate mofetil and isolation and subsequent decomposition of the said salts to the free acid by treatment with an acid (see D3 column 12 lines 35-57 and D6). The present claims 1-13 and 22, 23 can be considered new over D3 due to the exclusion of the present compounds (see column 4 lines 10-12) of the said document.

2.2 The present claims 14 and 15 relate to mycophenolate mofetil as the free base which is disclosed in the prior art D1-D6. It has to be pointed out that a document disclosing a chemical compound and its preparation made this compound available to the public in all grades of purity. Consequently the subject matter of claims 14 and 15 on file is not novel.

2.3 The claims 16-21 on file relate to the preparation of mycophenolate mofetil by reaction of a reactive intermediate of mycophenolic acid with 4-(2-hydroxyethyl)morpholine and isolation of the resulting mycophenolate mofetil by forming an acid addition salt and subsequently releasing the free base.

The prior art Documents D3(see column 16,line 60 to column 17 line20, example) and D8 (see page 4 line 36,lines 50 to page 5 line5, and page 5 line 50 to page 6 line 6 and page 9 line 27 to line 46 example 1), disclose the same process subject matter of the said claims 16-21. Furthermore it has to be pointed out that according to D3 and D8 the 4-(2-hydroxyethyl) morpholine is added under controlled conditions (see cited examples).

Consequently the present claims 16-21 on file are not new.

2.4 The prior art document D8 discloses oxalic salts of mycophenolate mofetil (see D8 page 4 lines 13-20 and is therefore prejudicial to the Novelty of the present claims 23 and

24.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 16-21 and 24, 25 is not new in the sense of Article 33(2) PCT.

3. Inventive step(Art.33(2)PCT)

3.1 The object of the present claims 1-13 is to provide a process for the purification of mycophenolate mophetil.

3.2 The experimental data comprised in the application show that the present invention provides an efficient process for the preparation of of high purity mycophenolate mophetil(I). Nevertheless the prior art document D3 and D7 disclose the preparation of base addition salts with amines of a structurally similar compounds (I) which salts precipitate spontaneously or may be isolated by extraction and further transformed to the free compound by treating with a stoichiometric amount of an acid which can be isolated by conventional methods. It appears therefore evident to the person skilled in the art wishing to provide an alternative process of purification of the said compound (I) to apply the reaction sequence described in D3 and D7. An Inventive step cannot therefore be acknowledged. for the present claims 1-13.

3.3 The object of the present claims 13-23 is to provide a process for the preparation of mycophenolate mophetil.

3.4 The experimental data comprised in the application show that the present invention provides an efficient process for the preparation of of high purity mycophenolate mophetil(I).

3.5 The prior art documents D3, D6 and D7 are considered to represent the closest state of the art for the assessment of Inventive step. The said prior art documents disclose the same process for the preparation of mycophenolate mophetil or analogues thereof. An inventive step cannot therefore be acknowledged for the said claims 16-23.

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